REMARKS

Statement of Substance of Interview – 37 C.F.R. § 1.133

In accordance with 37 C.F.R. § 1.133, Applicants submit herein a record of substance of the interview held on January 19, 2012 between Rebecca Hays and Stephanie Vavra for Applicants, and Examiners Robert Yamasaki and Ralph Gitomer.

The Llinas reference was discussed with respect to the inherent anticipation rejection. Applicants' representatives explained the legal standard for inherency and their view that in failing to cite any extrinsic evidence tending to show inherency, the Examiner had not met the burden for inherency set forth in *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). The Examiner suggested amending the claims to recite cell types, agent concentrations, or parameters of cholesterol modulation.

Status of the Claims

With the present communication, claim 26 is amended, and claims 29-43 are added. No claims are canceled and no new matter is added. Support for the amendment and new claims can be found throughout the specification as filed, including at pages 15-18 (Examples 1-6). Upon entry of the present amendments, claims 1-21, 26, 27, and 29-43 will be pending in this application, with claims 26, 27, and 29-43 under examination. Applicants respectfully request reconsideration of the application for the reasons that follow.

Claim Rejections – 35 USC § 102

Claims 26 and 27 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 4,897,426 to Llinas, *et al.*, ("Llinas"). Llinas teaches methods of blocking calcium low-threshold channels comprising the administration of aliphatic alcohols. Llinas at abstract. The Examiner asserts that Llinas teaches the administration of octanol to cells or mammalian subjects at concentrations that "coincide with the range shown in the specification to modulate

cholesterol levels," and that Llinas teaches administering octanol to a mammal in sufficient quantities to generate a blood concentration "of up to 1 mM." Office Action , p. 2. The Examiner asserts that Llinas teaches each of the steps of the pending claims, and that the Llinas methods "would be expected to increase or decrease cellular cholesterol levels as recited in the instant claims," such that "Llinas inherently anticipates the pending claims." *Id.* at p. 2-3. Applicants traverse the rejection for the reasons that follow.

Amended claim 26 recites:

> A method of modulating a cholesterol level of a cell comprising contacting one or more cells with an effective amount of octanol, or octanol and one or more of ceramide, diglyceride and lysophosphosphatidylcholine, for a sufficient time to:
>
> (a) induce re-localization of cholesterol from the plasma membrane to the endoplasmic reticulum, and/or
>
> (b) induce re-localization of cholesterol from the endoplasmic reticulum to the plasma membrane, and/or
>
> (c) decrease the total cholesterol level
>
> of the one or more cells.

As stated in the M.P.E.P., "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131, quoting *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). If the alleged anticipation is based on inherency, it must be supported by a rationale or evidence tending to show inherency. To establish inherency, "the *extrinsic evidence* 'must make clear that the missing descriptive matter is *necessarily present* in the thing described in the reference, and that it would be *so recognized* by persons of ordinary skill. Inherency, however, *may not be established by probabilities or possibilities*. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added; internal citations omitted). In this case, the

Examiner has mischaracterized the teachings of the cited art and has not met the evidentiary burden for a rejection based on inherency.

The Examiner has misapprehended the teachings of Llinas with respect to the concentration of octanol disclosed. Llinas teaches the administration of octanol in sufficient quantities to generate a blood concentration of **1 μM** (10^{-6} M), not 1 mM (10^{-3} M) as the Examiner asserts. Examples 3 and 4 of the present application show that cholesterol modulation was measured in response to 0.2-0.8 mM octanol, which is a 200-800 fold higher concentration than disclosed in Llinas. Application, p. 17, Fig. 4. Llinas clearly states at Table 1, col. 7, that the "[p]referred highest molar concentration[s]" of octanol for use in the disclosed methods is "10^{-6} M." Because the concentrations of octanol disclosed in Llinas are substantially lower than those of the present application, there is no basis to conclude that the Llinas methods would necessarily result in modulation of cholesterol levels.

The Examiner has cited no extrinsic evidence that the missing subject matter is necessarily present in the cited art or that it would be so recognized by one of ordinary skill in the art. Rather, the Examiner has assumed that the Llinas methods would inherently modulate cholesterol levels based solely on the fact that the methods comprise octanol administration to animal subjects. The Examiner suggests that because Llinas uses an octanol stock solution of a higher concentration than described in the pending application, cholesterol modulation would occur in cells near the site of injection. Office Action, p. 2-3. In the Examiner's own words, "the method of Llinas *would be expected* to increase or decrease cellular cholesterol levels as recited in the instant claims." Office Action, p. 3 (emphasis added). This *does not* meet the Federal Circuit standard for inherency.

The method of claim 26 comprises contacting one or more cells with an effective amount of the recited agents "for a sufficient time to (a) induce re-localization of cholesterol from the plasma membrane to the endoplasmic reticulum, and/or (b) induce re-localization of cholesterol from the endoplasmic reticulum to the plasma membrane, and/or (c) decrease the total cholesterol level of the one or more cells." The specification demonstrates that time sufficient

for cholesterol re-localization is on the order of minutes, and time sufficient for decreasing the total cholesterol level of a cell is on the order of hours. Specification, p. 15-18 (Examples 1-6).

Example 9 of Llinas describes the effects of octanol injected intraperitoneally on the function of inferior olivary (I.O.) neurons of the rat brainstem, as indicated by tremors in the platysma muscle of the face. Llinas, col. 2, line 3; col. 12, lines 31-50. Clearly, the 10 mM octanol stock solution administered in that example *must dissipate* from the point of injection in order for the experiment to succeed. Indeed, Llinas indicates that the injection is "given to create a concentration of 9.3 micrograms/g of rat body weight or $7x10^{-5}$ M in the vicinity of the neuronal cells (if all the alcohol was to be absorbed, and none metabolized)." Llinas at col. 12, lines 61-64. Hence, cells near the site of injection are exposed to high concentrations of octanol only transiently. Llinas does not disclose the rate at which the octanol dissipates from the site of injection, whether or how much octanol is metabolized or absorbed, or the time at which muscle tracings are taken relative to octanol administration. There is therefore no basis to conclude that cells near the injection site would be contacted with an effective amount of agent for a sufficient time to accomplish the cholesterol modulation recited in claim 26. For at least this reason, the pending claims are not inherently anticipated by Llinas.

Because Llinas does not expressly or inherently teach all of the elements of claim 26, the reference does not anticipate the pending claims. Accordingly, Applicants request that the rejection be withdrawn.

Conclusion

Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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